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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/764,110	12/06/96	CHEN	Y

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HM12/1120

EXAMINER	
BERCH, M	
ART UNIT	**PAPER NUMBER**
1624	26

DATE MAILED: 11/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/764,110	Chen
Examiner	**Group Art Unit**
Mark L. Berch	1624

☒ Responsive to communication(s) filed on *Oct 10, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-4, 8-10, 12-14, 18-21, and 23-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-4, 8-10, 12-14, 18, 20, 21, and 23-25* is/are rejected.

☒ Claim(s) *19* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *25*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on 10/10/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/764110 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants are reminded that deletions from the claims must be done by means of brackets. Material was removed in at least two places from the R^5 definition without use of brackets.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 8-10, 12-14, 18, 20, 21, 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "these moieties" at page 4 line 4 is unclear. It could mean a) the most immediately discussed set, viz., the $(C_1\text{-}C_4)$ alkyl or $(C_1\text{-}C_6)$ alkyl groups wherein one or two C-C single bonds were replaced by double or triple bonds or b) the $(C_1\text{-}C_4)$

alkyl or (C_1-C_6) alkyl groups themselves or c) the entire list of R^4 choices, e.g. the (C_1-C_2) alkyl piece at the very lend of page 3.

2. The use of R^{12} at page 4, line 13 is unclear. The variable is not specifically defined. It is not seen that it is needed. Deletion of the term is suggested to resolve this issue.

3.The ring at the twelfth from last line of page 3 is unclear. It starts by saying that the ring is "saturated" but then says that it may optionally have 1-3 double bonds. But a ring which is saturated, while it could optionally have e.g. substituents, it could not optionally have double bonds, since then it would no longer be saturated, but would be unsaturated.

4. Similarly, the eleventh from last line of page 3 says "contains a single heteroatom" and that means exactly one. But later in the paragraph, one or two O/S can appear, which is inconsistent. Further, that same line says that the ring "is carbocyclic" but later on there is the provision for heteroatoms. A carbocyclic ring cannot have heteroatoms.

5. The inclusion of "inflammatory disease" now means that other terms appear to be superfluous. Thus, the very next term is an inflammatory disease, and hence is already included by the new term. It is correct that this problem can be solved by removing all inflammatory disorders, and placing them in a dependent claim.

6. A similar problem occurs with "depression" which is a generic term which covers other choices such as postpartum depression. In fact, something like "bipolar disorder" would be covered by both "depression" and "major depressive disorder".

The use of repeating coverage of the same disorders makes it unclear what is actually intended. Thus, for example, since "depression" covers "single episode depression", why is the latter present? Or does the former not cover the latter?

7. These choices are indefinite: hemorrhagic stress, cyclothymia and recurrent depression. The examiner has checked the two largest medical dictionaries (Online Medical Dictionary and Steadman's Medical Dictionary), each of which has thousands of entries, and none of these three appeared in either text. That is prima facie evidence that these terms do not have a well defined meaning. If applicants disagree, they are invited to present a clear definition from a standard text.

8. The "either" of the 6th line below Formula I is not correct and should be deleted. If D is carbon, it must be double bonded to E.

9. The "when it is single bonded to E" of the 7th line below Formula I is not correct and should be deleted. It is always single bonded to E.

10. Similarly, the "or F" seven lines later is incorrect. Nothing can be double bonded to F.

11. Fatigue Syndrome is not the accepted term; it is assumed that Chronic Fatigue Syndrome is intended; the claims should be amended accordingly

12. An HIV infection is not a disorder; it needs its own category. A disorder is a disturbance in the regular and natural functions of either body or mind. An infection is not part of the regular and natural functions of either body or mind and hence it is not a disturbance in it. Of course, an infection can trigger a disorder, such as a fever

or damage to the immune system. Thus, the fever is the disorder, not the infection. The infection is the cause of the disorder, but not the disorder itself. Not all bodily problems are disorders. Things like infections and wounds (e.g. bee sting) can subsequently cause a disorder, but are not themselves a disorder. Applicants' traverse on this point is unpersuasive. A sting, or an infection, is not a disturbance in the function of the body because a sting, or a virus is not part of the body in the first place. The sting is a wound, not a disorder. The sting in turn causes e.g swelling and the swelling is the disorder. An HIV infection causes a fever, and a fever is the disturbance. Being hit by a ball is not a disorder, but the resulting "head trauma" is a disorder. As for a solution, this ground can be overcome simply by taking it out of the "disorder" category and writing "c) HIV infection".

13. The term (a) language is vague. Its scope is unknown. Determining whether a given disease responds or does not respond to such antagonism will surely involve undue experimentation. Suppose that a given CRF Antagonist X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is

significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another antagonist Y is potent enough, so that D really does fall within the claim. Thus, how many different antagonists must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10

responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Indeed, it is not clear that there is any disorder that one can state with confidence does not fall within the claim. Hence, the claim is indefinite. Applicants' previous traverse on this point is unpersuasive. The examiner is not requiring "applicant to test each and every embodiment of the invention". The examiner isn't suggesting that applicant test anything here. The examiner is doing the reverse --- noting that this sort of claim language forces on the public a potentially unlimited series of tests to determine the scope of the claim. The actual scope of term (a) is simply not known at present; for all we know, every disease --- or none --- fall into this category. Determining the actual scope of this term, at this point in time, requires extensive and fundamental research, which is improper to place on the public. The burden is on applicant to particularly point out and distinctly claim the scope of the invention. Except for experimentation of a routine nature, this burden cannot be placed on the public, and that is exactly what this language does. For the reasons set forth in the lettered points above, determining for sure which diseases do and which do not fall within the ambit of this language is a difficult undertaking, one that is not impossible but one that involves undue experimentation. Applicants had mentioned animal tests. These are useful, but an animal test does not determine

whether a disease falls within this category; it merely identifies which drugs might be successful for a given disease. The question here is the meaning of the claim language, not whether any given compound will be effective against any given disease.

Applicants now state that whether or not this or that disease falls within the claim can be determined "by referring to the state of the art at the time of contemplating using one of the compounds". First, the determination is made at present. More importantly, "the art" that applicants refer to simply does not exist. For example, there is no standard text one can go to to determine which diseases do and do not fall within this category. That is because of the lack of knowledge of CRF. This is not a situation like e.g. hypertension where the conditions which are embraced and are not embraced have been worked out already. The situation here is one of unknown scope. If applicants disagree, they are invited to present references which show that one of ordinary skill in the art would know what the term does and does not include. Which disorders, if any, are there which applicants can confidently state does not fall within choice a), other than disorders which the Chalmers and Stratakis references teach arise from unduly low levels of CRF? What about disorders about which very little is known about cause, e.g. various idiopathic disorders? Considering that CRF antagonists are not being used as medicinals, how much confidence can there be that any such "prior art" list being complete? Is applicant saying that if it isn't on any list or set of lists, it isn't included? If the answer is no, then of what value is the list in answering the question: What is <u>not</u> included?

Claims 2-4, 8-9, 12-14, 18, 20, 21, 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The replacement of the term "thioalkyl" with "alkylthio" is clearly new matter. "Thioalkyl" is not standard nomenclature. Thio as a generic prefix simply indicating the presence of sulfur. It is of course possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could even possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. CH_3-S-CH_2- or possibly the sulfur could be a double bonded substituent rather than a single bonded one, e.g. CH_3-C(=S)-CH_2- This specification gives no clear evidence as to which of these plausible choices was originally intended. Applicants' traverse on this point is unpersuasive. Applicants argument is basically that, had they intended mercaptoalkyl, they could have "incorporated" it into the alkyl onto which it was substituted. But the fact that this was another way of doing it doesn't prove that this wasn't applicants intent all along. Further, this incorporation statement simply isn't true. Using the (C_1-C_4) alkyl base moiety as an example, the mercapto(C_1-C_3)alkyl substituted onto this (C_1-C_4) alkyl does not work out to the same as mercapto(C_1-C_7)alkyl. The claim permits two such mercapto(C_1-C_3)alkyl substituents on the (C_1-C_4)

alkyl, which would come out to dimercapto(C_3-C_{10})alkyl. That is, the current claim language, understanding thioalkyl as mercapto(C_1-C_3)alkyl, could yield the dimercapto(C_3-C_{10})alkyl (although the two mercapto groups themselves would have to be on different carbons). Further, using mercapto(C_1-C_7)alkyl rather than (C_1-C_4) alkyl substituted by mercapto(C_1-C_3)alkyl has a second difference. The claim language does not require that the two substituents be the same. Thus, the current claim language, understanding thioalkyl as mercapto(C_1-C_3)alkyl, would give (C_1-C_4) alkyl substituted by mercapto(C_1-C_3)alkyl and by CN, provided of course that the CN is attached to the (C_1-C_4) alkyl, not the mercapto(C_1-C_3)alkyl. If one used the mercapto(C_1-C_7)alkyl approach, one would have to say mercapto(C_1-C_7)alkyl optionally substituted by the entire substituent list (except mercapto(C_1-C_3)alkyl) all over again. This would be awkward, and further, different, since that language would permit the CN to be attached to the same carbon as had the SH for example, not permitted by the current claim language. Third, the incorporation would not actually give mercapto(C_1-C_7)alkyl, since both the (C_1-C_4) alkyl and the mercapto(C_1-C_3)alkyl have a minimum of one carbon, but rather mercapto(C_2-C_7)alkyl, which would cause further complications. Thus, applicants' reasoning is unsound.

Claims 2-4, 8-9, 12-14, 18, 20, 21, 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The provision for "two or three substituents" on the pyrimidinyl in fourth from last line of page 4 is new matter. Page 5, line 12 says "more than two" not "two or more". With regard to the other argument, It may have been an error, but the material simply is not present in either locations. The same is true for the phenyl and pyridyl substituents at eighth from last line of page 4. That should be just 3 substituents, not 2 or 3.

Claims 2-4, 8-9, 12-14, 18, 20, 21, 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have added CF_3 to the R^4 definition. This has the same problems. Just an example, page 9 does not provide for a compound with R^3 as CN where R^4 is CF_3, but now the claim does. Applicants' traverse on this point is unpersuasive, because their reading of that paragraph is not agreed with. This covers a groups of compounds in which the variables are narrowed in the ways given. These are not alternative choices. Applicants are reading this as if it said R^3 is ... or R^4 is ... or G is .... etc. It does not say that. The choices are separated by semicolons. Semicolon does not mean "or"but rather it means "and".

Claims 20-21, 23-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The inclusion of "inflammatory disease" is new matter and lacking in description. Applicants note that this was in original claim 17. That is correct, but that is not in the specification. This problem can be solved by adding the terminology of claim 17 back into the specification

Claims 20-21, 23-24 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for many disorders, does not reasonably provide enablement for inflammatory disease, stroke and ischemic neuronal damage, depression, Fatigue Syndrome, rheumatoid arthritis, and postpartum depression, obesity, chemical dependencies and addictions, HIV infection, cancer, and Syndrome of Inappropriate Antidiuretic Hormone Secretion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A. Enablement for the scope of "inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no

common mechanism by which all, or even most, inflammations arise. Accordingly, treatments for inflammation are always tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent.

Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially Streptococcus pyogenes, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and Mycoplasma pneumoniae. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye)

is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to

reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness,

pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally

cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas,

Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when

shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and

pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. The notion that inflammation generally is even linked to CRF has no scientific basis; no such assertion is established in any reference of record. Thus, it is not reasonable to any agent to be able to treat inflammation generally.

B. Syndrome of Inappropriate Antidiuretic Hormone Secretion. This is a disorder of fluid and electrolyte balance cause by excessive release of ADH. It is normally treated by restriction of water, or by attacking the underlying case of the SIADH, such as

radiation or surgery to remove the tumor, or treatment of a CNS infection. Foster establishes that pharmacological treatment is via tetracycline antibiotics or diuretics (see pages 9-11). However, CRF antagonists have neither such property. Neither Stratakis nor Chalmers state that CRF antagonists would be expected to have such a property. Thus, it is not the case that CRF inhibitors as a class are recognized as having this property (see *Ex parte Sudilovsky*, 21 USPQ2d 1702). The same is true of the antibiotic property. It is thus clear that one of ordinary skill in the art knows how to treat SIADH only with these two methodologies, and hence treating it with CRF antagonists is beyond this skill level.

C. Cancer. The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus,

it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. Moreover, the vast majority of cancers are either untreatable, or are treated by cytotoxic agents, that is, compounds which kill cells. However, again, there is no evidence of record, or even assertions, that these CRF antagonists actually kill cells, let alone preferentially kill cancer cells.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Applicants dispute reliance on Ferens. But the decision states, "However, where an applicant predicates utility ... on allegations ... which are or border on the incredible in light of the contemporary knowledge, those allegations must be substantiated by acceptable evidence." The notion that a compound (let alone a genus of billions of compounds, as is the case here) can be effective against cancer generally does indeed border on being incredible. Attempts to find chemotherapeutic agents have been among the most intensive in the entire field of medicine, yet no agent has ever been found which comes even remotely close to such a goal. In fact, Peckam, ed., Oxford Textbook of Oncology, Volume 1, 1995, page 452 is cited for the fact that "the majority of common cancers do not respond" to chemotherapy. As examples, there

can be mentioned many of the carcinomas, such as those of the colon, rectum, renal cell, thyroid and hepatocellular, along with lung cancers such as squamous cell and adenocarcinoma. Thus, even if there were such an agent effective against all the cancers which do respond, it could not be said to be effective against cancer generally. And of course, there is no such agent, or even category of agents (such as "alkylating agents"). If applicants disagree, they are invited to name the agent. This then meets the standard of "there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." (*In re Langer*, 503 F.2d at 1391, 183 USPQ at 297) insofar as the "its scope" part is concerned.

There is an additional problem as well. No guidance is provided as to which cancer(s) the claimed compounds would be effective against. There is none in the specification or any reference cited. Further, DeVita, ed, "Cancer: Principles & Practice of Oncology, 5th Edition", 1997, index pages 24-25 are provided. This is a recent, massive (over 3000 pages) standard text on oncology. The index pages indicate that there is no mention in the index on the use of CRF antagonists for treatment of cancer. This is prima facie evidence that such guidance does not exist. Thus, there has not been provided proper instruction on how to use. This is required for enablement. See *In re Schmidt*, 153 USPQ 640 where "assist the liver function in hepatic disturbances" was considered insufficient because there are many different liver functions. There are of course far more cancers than there are liver functions. A similar problem rose in *In re Citron*, 139 USPQ 520. Further, *In re Brana* 34 USPQ2nd

1437, 1440 makes it clear that guidance for somewhere as to what sort of cancer is to be treated is essential.

With regard to *Citron*, applicants argue that it was not the large number of disorders, but the nature of them, and the unknown nature of the extract. This is not agreed with. The court listed the uses as set forth in the specification, a list which is substantially narrower than the list given here, and called it "practically a geriatric panacea". A panacea is a remedy for all diseases ... a cure-all. The court was clearly concerned with the scope. As for the "nature of the disorders claimed to be treated" the one singled out for such criticism was "several types of cancer", and that is the case here as well. As for concern about "the chemical nature and mechanism of action", the examiner cannot locate any such concern in the decision. Method claims are routinely given for compounds of unknown structure. Applicants are asked to point to the specific sentence(s) of the decision.

On page 18, applicants present the argument that "stress can be a contributing factor in cancer and that combating stress can therefore reduce the likelihood of cancer formation and propagation." However:

a) The claims are not drawn to the prevention of cancer, but the treatment of cancer. Applicants appear to be assuming that if a compound can be used to prevent cancer, then it can be used to treat cancer. Such an assumption, if being made, has absolutely no scientific basis whatsoever. If applicants disagree, they are invited to present the name of a compound which has been established as being both effective for treating

cancer and effective for preventing cancer. If treating cancer generally were simply a matter of reducing "psychological stress", then cancer would long ago have been treated, since there are many methods, both pharmacological and non-pharmacological, to reducing stress.

b) Even if true, the notion that cancers generally are caused by stress is again without any scientific basis. The claims are not limited to those cancers caused by stress, but to cancers generally.

c) Even if those two factors were overcome, those of ordinary skill in the art have no idea how to accomplish such a goal. That is, even if cancer can be treated by pharmacologically reducing stress, there is no evidence that one of ordinary skill in the art knows how to do this. No one has ever accomplished such a goal.

Applicants cite the 1993 news story by Fackelmann. The article, which is a general description of some research, makes no mention of either CRF antagonist or treatment of cancer. Applicants are drawing inferences which simply do not appear in the news article. Applicants cite Langlois as saying that "Pathologies that melatonin is involved" include "cancer" and "stress." It is of course true that in certain types of skin cancers, melatonin is involved. No one would possibly read that as saying that the compounds would be used for cancers generally or that stress causes cancer generally. Applicants also cited WO 99/11643. Aside from the fact that this is a published patent application and not a scientific paper, it must be also noted that the 1) the reference does not cite any research saying that these CRF antagonists can be

used to treat cancer and 2) the massive lists of utilities given at pages 7-8 does not include cancer.

Applicants also refer to a 101 rejection. No such rejection has been made here, nor has there been "an assertion of lack of utility". The question here is one of scope. D. Chemical dependencies and addictions. The same is true here. The notion that a compound could be effective against chemical dependencies in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug addiction" generally. That is because "drug addiction" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed. Again, if applicants disagree, they are invited to present a counter example.

Applicants consider this to be improper speculation. However, it is firmly grounded in the fact that there are very different receptors for some addictions. For

alcohol, no receptor has been found, so it is not known if alcohol addiction operates by receptor binding.

For example, the most important chemical addiction is to alcohol. There is no established pharmacological treatment of alcohol addiction. The closest are drugs which cause the user to become ill if they do consume alcohol, but that is obviously not a treatment per se. Applicants raise the question of Revia. REVIA blocks the opiate receptor, a property that the claimed compounds are not alleged to have. Indeed, no one has ever succeeded in finding a treatment for opiate addiction without blocking the opiate receptor. That alone is enough to be reason to doubt the efficacy of the claimed compounds for the treatment of opiate addiction. The reference also cites one study showing effectiveness of REVIA for treatment of alcoholism. Alcohol addiction is somewhat atypical because unlike benzodiazepines, nicotine, etc, it has not been shown to involve a particular receptor, and thus either does not involve or receptor, or that receptor has not been identified. This one study hardly establishes efficacy, but even if it did, that would be exactly two, hardly evidence of a general effect. Moreover, at the time of filing, and indeed, even at the present time, one of ordinary skill in the art has not been able to demonstrate that they know how to get Revia to work for alcoholics. It is possible that it may need to be combined with an SSRI to work. Addictions are in general one of the most difficult of all categories of pharmacological effects to achieve, evidence that the skill level in this art is low relative to difficulty of task. The treatment of addictions based on receptors (e.g.

cocaine, opiates, benzodiazepines) without actually blocking the receptor has so far proved to beyond the skill of practitioners in the art, and there is no reason to think that these compounds are capable of doing this. Applicants assertion that these addictions can be treated without blocking the receptor is contrary to everything which is known about receptor based addictions. That provides the *Langer* standard set forth above. Applicants state, " the compound does not necessarily have to interact with a particular receptor or receptor" and "it is not incredible that a single drug could be useful in treating addictions ... generally." The examiner has not said that this is incredible. However, the skill level in the art, at present, is such that either goal (treatment of receptor based addictions without blocking the receptor and a single drug to treat addictions and chemical dependencies generally) is beyond the skill level of the art, as seen by the fact that huge amounts of efforts in this field have not produced such a result.

Applicants cite Ciccocioppo. It is not seen how this paper can possible establish enablement for the claimed compounds. The paper deals with the serotonin system and the serotonic receptors. Some drugs, specifically alcohol, cocaine and nicotine may well have usable links to this. Other drugs, e.g. benzodiazepines and marihuana, apparently are not. So how could this help with drugs generally? Further, the claimed compounds are not asserted to be active at any 5-HT receptor, and the paper makes no mention of CRF antagonists, so how will this help applicants? Further, the paper is raising some possibilities. The final paragraph makes clear that

the skill level in this art is extremely low ("not much is known ... this lack of information has severely limited ... more studies are therefore needed...")

This is even more so for Tranxene, which isn't alleged to treat alcohol addiction, but rather for providing for symptomatic relief of alcohol withdrawal, which is quite a different thing. Applicants cite a reference on Tranxene, which is indicated for the relief of alcohol withdrawal. But this is a standard benzodiazepine-based antianxiety drug; it acts by activating the BZ receptor. Why should a CRF antagonist be expected to do what Tranxene can do? Applicants argument is not understood. Which addiction or set of addiction is this drug asserted to treat, and to what degree, if any, is this relevant to CRF antagonists?

E. HIV infection. No one has ever been able to treat any HIV infection --- indeed, any viral infection at all, except by means of an antiviral, something that disrupts the operation of the virus itself. There is no reason to think that a CRF antagonist could possibly do this, since no virus actually uses this hormone for any aspect of its replication, infectivity, etc.

Applicants cite Kinchington. But the last sentence on page 91 simply says that, as of 1999, other things (a list which does not include CRF antagonists) "have been investigated." It doesn't say that anyone has been able to figure out how to get them to work. What is known to one of ordinary skill in the art is in fact listed on page 90, and every single one of these is an antiviral. It is of course entirely possible that, some day, the HIV infection could be treated with e.g. cytokines. However, a) as of the

filing date, that skill level was not reached yet, and b) applicants compounds are not cytokines. No copy of Zou was provided. With regard to the other references, applicants are reminded that the claim does not refer to AIDS. Applicants state, "it is not incredible to treat immune suppression using a CRF antagonist." But the claim is drawn to the HIV infection itself, not the immune suppression that is characteristic of the AIDS that results from the HIV infection. This reasoning confuses cause and effect. Thus, if a puncture wound can cause lockjaw, something effective against lockjaw doesn't necessarily help in treating a puncture wound.

F. Obesity. Chalmers is cited as an example of the skill level in this art as of 1996. Note especially pages 171-172, which deal with "Therapeutic Strategies". Eating disorders, especially obesity are associated with abnormally low levels of CRF. Therefore, administration of CFR antagonists, if they had any effect, would be expected to make matters worse. That is the clear teaching of the reference. Applicants' traverse on this point is unpersuasive. Applicants state that treatment of obesity is not itself "incredible" and that treating obesity is "substantial". Agreed. But no 101 rejection is being made. This is a lack of enablement. Chalmers gives reason "for one skilled in the art to question the objective truth of the statement of utility" because Chalmers teaches the exact opposite. Chalmers says (see e.g. Figure 4) that the strategy for obesity is to raise CRF, but applicants' compounds are disclosed to suppress CRF.

G. Fatigue Syndrome, rheumatoid arthritis, and postpartum depression. The same reasoning applies here, except that the Stratakis reference is relied on. Again it lists disorders with low CRF, including chronic fatigue, in the second sentence in the second full paragraph of page 207. Another such list appears in the last full paragraph on page 206, which specifically lists rheumatoid arthritis, and postpartum depression as being "hypoarousal states". Thus, going by what little was known at the time, one would expect that, if such agents work at all, they would be expected to make matters worse, not better.

H. Depression. See the previous point. Page 206 of Stratakis lists three types of depression, viz. postpartum depression, seasonal depression, and the depression following the cessation of smoking as being "hypoarousal states" which, if correct, these compounds would be expected to worsen.

I. Stroke and ischemic neuronal damage. Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at

the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the are of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well. These have not succeeded, and thus ischemic neuronal damage is also included.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining treatment of stroke was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there was cited Chalmers which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." As an example of this massive effort, Pentoxifylline has been one of the most intensely studied, with literally dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Yet, it is still unclear whether this drug can be made to prevent stroke. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. The considerable difficulty of getting a clear answer for this drug is abundant evidence that the skill level in this art is low relative to the difficulty of task. Applicants' compounds have been subjected to no such study.

Applicants previously cited Owens, a large review article on CRF. As this is an older (1991) reference, it cannot supply information about the state of the art at the time of the invention. However, it is instructive to note the last two sentences of the

text. This states explicitly that the research necessary to understand "basic CRF physiology" remains to be done, and that "pharmacological agents" are only "possibilities", not realities. Also cited was Kappelle, but the Kappelle abstract can hardly be said to support applicants' case, as it notes, "Several neuroprotective compounds have been studied, but at this moment [1997] none of these has definitely been proved effective." and "Treatment of acute ischemic stroke is uncertain." Applicants note that Kappelle lists acetylsalicyclic acid (aspirin) warfarin, etc. This misses the point. The stroke itself (which involves extensive damage to neurons and consequent loss of brain function) at time of filing and at present time, cannot be treated, showing difficulty of task. The only medicines available are those to prevent the stroke. Thus, local or systemic thrombolytic agents are use to provide clot lysis -- in other words, prevent the blood clot from forming or break it up quickly, so you can prevent the stroke's damage. Thus, aspirin can be given daily, or TPA can be given immediately after the first symptoms, both to head off the stroke. Kappelle uses the phrase "prevention of future cardiovascular complication". Further, even if these were treatment of stroke, it would not help applicants. Applicants compounds are not disclosed to be thrombolytic, and hence, if all one of ordinary skill in the art knows is thrombolytics, then such use with these CRF antagonists is beyond their skill level.

When operativeness has been properly challenged, it is incumbent on applicant to limit the claims accordingly, cf. *In re Harwood*, 156 USPQ 673, *In re Cook*, 169

USPQ 298, I*n re Langer*, 183 USPQ 288, *In re Corkill*, 226 USPQ 1005, 1009, and *In re Rainier*, 153 USPQ 802.

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718.

Mark L. Berch

Primary Examiner

Group 1620 - Art Unit 1624

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